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=> s antisense or anti-sense or (complem? (2n) (oligonucl? or nucle?))  
2 FILES SEARCHED...  
3 FILES SEARCHED...  
L6 157727 ANTISENSE OR ANTI-SENSE OR (COMPLEM? (2N) (OLIGONUCL? OR NUCLE?)  
)

=> s ((cAMP (n) dependent protein kinase) or (protein kinase A) or PKA) (5n) (rII  
or r2)

L7 1455 ((CAMP (N) DEPENDENT PROTEIN KINASE) OR (PROTEIN KINASE A) OR  
PKA) (5N) (RII OR R2)

=> s 16 and 17

L8 74 L6 AND L7

=> dup rem 18

PROCESSING COMPLETED FOR L8

L9 35 DUP REM L8 (39 DUPLICATES REMOVED)

=> s 19 and py<=2001

4 FILES SEARCHED...

L10 25 L9 AND PY<=2001

=> s 110 and (16 (p) 17)

L11 19 L10 AND (L6 (P) L7)

=> d 111 ibib abs 1-19

L11 ANSWER 1 OF 19 MEDLINE on STN

ACCESSION NUMBER: 1999098903 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9880537

TITLE: Dynamic complexes of beta2-adrenergic receptors with  
protein kinases and phosphatases and the role of gravin.

AUTHOR: Shih M; Lin F; Scott J D; Wang H Y; Malbon C C

CORPORATE SOURCE: Department of Molecular Pharmacology, Diabetes & Metabolic  
Diseases Research Program, University Medical Center, State  
University of New York, Stony Brook, New York 11794-8651,  
USA.

SOURCE: Journal of biological chemistry, (1999 Jan 15)  
274 (3) 1588-95.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990223

Last Updated on STN: 19990223

Entered Medline: 19990211

AB Signals mediated by G-protein-linked receptors display agonist-induced  
attenuation and recovery involving both protein kinases and phosphatases.  
The role of protein kinases and phosphatases in agonist-induced  
attenuation and recovery of beta-adrenergic receptors was explored by two  
complementary approaches, **antisense** RNA suppression and  
co-immunoprecipitation of target elements. Protein phosphatases 2A and 2B  
are associated with the unstimulated receptor, the latter displaying a  
transient decrease followed by a 2-fold increase in the levels of  
association at 30 min following challenge with agonist. Protein kinase A  
displays a robust, agonist-induced association with beta-adrenergic  
receptors over the same period. Suppression of phosphatases 2A and 2B  
with **antisense** RNA or inhibition of their activity with  
calyculin A and FK506, respectively, blocks resensitization following  
agonist removal. Recycling of receptors to the plasma membrane following  
agonist-promoted sequestration is severely impaired by loss of either  
phosphatase 2B or protein kinase C. In addition, loss of protein kinase C  
diminishes association of phosphatase 2B with beta-adrenergic receptors.  
Overlay assays performed with the **RII** subunit of **protein**  
**kinase A** and co-immunoprecipitations reveal proteins of  
the A kinase-anchoring proteins (AKAP) family, including AKAP250 also  
known as gravin, associated with the beta-adrenergic receptor.  
Suppression of gravin expression disrupts recovery from agonist-induced  
desensitization, confirming the role of gravin in organization of

G-protein-linked signaling complexes. The Ht31 peptide, which blocks AKAP protein-protein interactions, blocks association of beta-adrenergic receptors with protein kinase A. These data are the first to reveal dynamic complexes of beta-adrenergic receptors with protein kinases and phosphatases acting via an anchoring protein, gravin.

L11 ANSWER 2 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 97242213 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9125203  
TITLE: Type II protein kinase A up-regulation is sufficient to induce growth inhibition in SK-N-SH human neuroblastoma cells.  
AUTHOR: Kim S N; Lee G R; Hwang E S; Lee J H; Park S D; Cho-Chung Y S; Hong S H  
CORPORATE SOURCE: Department of Molecular Biology, Seoul National University, Republic of Korea.  
SOURCE: Biochemical and biophysical research communications, (1997 Mar 17) 232 (2) 469-73.  
Journal code: 0372516. ISSN: 0006-291X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199704  
ENTRY DATE: Entered STN: 19970506  
Last Updated on STN: 19990129  
Entered Medline: 19970422

AB We have previously reported that overexpression of **RII** beta subunit of **protein kinase A**, which markedly reduces RI alpha protein, induces growth inhibition in SK-N-SH human neuroblastoma cells. To determine whether the reduction of RI alpha or protein kinase A isozyme type I is essential in the growth inhibition of SK-N-SH cells, we overexpressed RI alpha in sense and **antisense** orientation. Type I protein kinase A activity was increased in the RI alpha-overexpressing cells and was decreased in the RI alpha **antisense**-expressing cells. However, the changes in type I protein kinase A activities did not affect cell growth. Overexpression of RII beta or C alpha increased type II protein kinase A and inhibited cell growth in both cell lines regardless of the type I protein kinase A level. These results indicate that type II protein kinase A is the main effector in the cAMP-mediated growth regulation of SK-N-SH human neuroblastoma cells.

L11 ANSWER 3 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 95034379 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7947390  
TITLE: Retroviral vector-mediated overexpression of the **RII** beta subunit of the **cAMP-dependent protein kinase** induces differentiation in human leukemia cells and reverts the transformed phenotype of mouse fibroblasts.  
AUTHOR: Tortora G; Budillon A; Yokozaki H; Clair T; Pepe S; Merlo G; Rohlf C; Cho-Chung Y S  
CORPORATE SOURCE: Cellular Biochemistry Section, National Cancer Institute, NIH, Bethesda, Maryland 20892.  
SOURCE: Cell growth & differentiation : molecular biology journal of the American Association for Cancer Research, (1994 Jul) 5 (7) 753-9.  
Journal code: 9100024. ISSN: 1044-9523.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199412  
ENTRY DATE: Entered STN: 19950110  
Last Updated on STN: 20000303  
Entered Medline: 19941207

AB We have recently shown, using **antisense** strategy, that the **RII** beta regulatory subunit of **cAMP-dependent protein kinase** is essential for cAMP-induced growth inhibition and differentiation of HL-60 human leukemia cells. We constructed a retroviral vector for RII beta (MT-RII beta) by inserting human RII beta complementary DNA into the OT1521 retroviral vector plasmid that contains an internal mouse metallothionein-1 promoter and a neomycin resistance gene. The PA317 packaging cell line was then transfected with MT-RII beta plasmid to produce the amphotrophic stock of MT-RII beta retroviral vector. The infection with MT-RII beta and treatment with CdCl2 brought about growth arrest in HL-60 human leukemia and Ki-ras-transformed NIH 3T3 clone DT cells in monolayer culture with no sign of toxicity. The growth inhibition correlated with the expression of RII beta and accompanied changes in cell morphology; cells became flat, exhibiting enlarged cytoplasm. The growth of these cells in semisolid medium (anchorage-independent growth) was almost completely suppressed. In contrast, overexpression of the RI alpha subunit of protein kinase enhanced the cell proliferation in DT cells. The MT-RII beta-infected cells exhibited an increased sensitivity toward treatment with cAMP analogues, such as 8-Cl-cAMP and N6-benzyl-cAMP, as compared with the parental noninfected cells. In MT-RII beta HL-60 cells, N6-benzyl-cAMP treatment greatly enhanced the expression of monocytic surface markers. These results suggest that the RII beta cAMP receptor, by binding to its ligand, cAMP, acts as a tumor suppressor protein exerting growth inhibition, differentiation, and reverse transformation.

L11 ANSWER 4 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 94323884 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8047985  
TITLE: Experimental gene therapy of human colon cancer.  
AUTHOR: Bold R J; Warren R E; Ishizuka J; Cho-Chung Y S; Townsend C M Jr; Thompson J C  
CORPORATE SOURCE: Department of Surgery, University of Texas Medical Branch, Galveston 77555-0533.  
CONTRACT NUMBER: 5R37 DK15241 (NIDDK)  
PO1 DK35608 (NIDDK)  
SOURCE: Surgery, (1994 Aug) 116 (2) 189-95; discussion 195-6.  
Journal code: 0417347. ISSN: 0039-6060.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199408  
ENTRY DATE: Entered STN: 19940909  
Last Updated on STN: 20000303  
Entered Medline: 19940830

AB BACKGROUND. Gastrin regulates growth of human colon cancer cells by activation of the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA). Gastrin and 8-Br-cAMP, a membrane-permeable cAMP analog, inhibit growth of HCT116 cells; both stimulate growth of LoVo cells. This dual effect on growth may be explained by relative amounts of the regulatory subunit (RI alpha or **RII** beta) of **PKA** within the cancer cells. **Antisense** oligodeoxynucleotides (ASO) to either RI alpha or RII beta inhibit protein translation of the target mRNA by sequence-specific binding; subsequently, cellular PKA content and the cAMP-mediated growth may be altered. We determined whether ASO to either the RI alpha or RII beta subunit altered the cAMP-mediated growth of HCT116 and LoVo human colon cancer cells. METHODS. HCT116 cells were

treated with RII beta ASO (15 mumol/L, 4 days) and then treated with 8-Br-cAMP (25 mumol/L); tritiated thymidine incorporation was measured after 24 hours, and the cell number was determined on alternate days. Protein and mRNA levels of the RII beta subunit were determined by Western and Northern blotting, respectively. Similar studies with an ASO against the RI alpha subunit were performed on LoVo cells. RESULTS. RII beta ASO reversed the cAMP-mediated inhibition of growth of HCT116 cells, and RII beta ASO decreased the protein level of the RII beta subunit. RII beta ASO did not alter the basal growth of HCT116 cells. RI alpha ASO reversed the cAMP-mediated stimulation of growth of LoVo cells. CONCLUSIONS. The regulatory subunits of PKA are potential targets to alter growth of human colon cancer cells. Gene therapy directed to alter specific steps in signal transduction pathways may provide new therapeutic strategies.

L11 ANSWER 5 OF 19 MEDLINE on STN  
 ACCESSION NUMBER: 94294479 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8022860  
 TITLE: The regulatory subunit of cAMP-dependent protein kinase as a target for chemotherapy of cancer and other cellular dysfunctional-related diseases.  
 AUTHOR: Cho-Chung Y S; Clair T  
 CORPORATE SOURCE: Cellular Biochemistry Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.  
 SOURCE: Pharmacology & therapeutics, (1993 Nov) 60 (2) 265-88. Ref: 171  
 Journal code: 7905840. ISSN: 0163-7258.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199408  
 ENTRY DATE: Entered STN: 19940815  
 Last Updated on STN: 20000303  
 Entered Medline: 19940804

AB Three separate experimental approaches, using site-selective cAMP analogs, **antisense** strategy and retroviral vector-mediated gene transfer, have provided evidence that two isoforms, the RI- and **RII**-regulatory subunits of **cAMP-dependent protein kinase**, have opposite roles in cell growth and differentiation; RI being growth stimulatory while RII is a growth-inhibitory and differentiation-inducing protein. As RI expression is enhanced during chemical or viral carcinogenesis, in human cancer cell lines and in primary human tumors, it is a target for cancer diagnosis and therapy. 8-Cl-cAMP and RI **antisense** oligodeoxynucleotide, those that effectively down-regulate RI alpha and up-regulate RII beta, provide new approaches toward the treatment of cancer. This approach to modulation of RI vs RII cAMP transducers may also be beneficial toward therapy of endocrine or cellular dysfunction-related diseases where abnormal signal transduction of cAMP is critically involved.

L11 ANSWER 6 OF 19 MEDLINE on STN  
 ACCESSION NUMBER: 91367871 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1653961  
 TITLE: Role of site-selective cAMP analogs in the control and reversal of malignancy.  
 AUTHOR: Cho-Chung Y S; Clair T; Tortora G; Yokozaki H  
 CORPORATE SOURCE: Cellular Biochemistry Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.  
 SOURCE: Pharmacology & therapeutics, (1991) 50 (1) 1-33.  
 Ref: 346  
 Journal code: 7905840. ISSN: 0163-7258.  
 PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199110  
ENTRY DATE: Entered STN: 19911103  
Last Updated on STN: 19970203  
Entered Medline: 19911017

AB Two isoforms of cAMP receptor protein, RI and RII, the regulatory subunits of **cAMP-dependent protein kinase**, transduce opposite signals, the RI being stimulatory and the RII being inhibitory of cell proliferation. In normal cells RI and RII exist at a specific physiological ratio whereas in cancer cells such physiological balance of these receptor proteins is disrupted. Reversal and suppression of malignancy can be achieved when the physiologic ratio of these intracellular signal transducers of cAMP is restored as shown by the use of site-selective cAMP analogs, **antisense** oligodeoxynucleotides or gene transfer, suggesting new approaches to cancer control.

L11 ANSWER 7 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 90138896 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1689049  
TITLE: An **antisense** oligodeoxynucleotide targeted against the type II beta regulatory subunit mRNA of protein kinase inhibits cAMP-induced differentiation in HL-60 leukemia cells without affecting phorbol ester effects.  
AUTHOR: Tortora G; Clair T; Cho-Chung Y S  
CORPORATE SOURCE: Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.  
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1990 Jan) 87 (2) 705-8.  
Journal code: 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199003  
ENTRY DATE: Entered STN: 19900328  
Last Updated on STN: 19970203  
Entered Medline: 19900306

AB The type II beta regulatory subunit of **cAMP-dependent protein kinase** (RII beta) has been hypothesized to play an important role in the growth inhibition and differentiation induced by site-selective cAMP analogs in human cancer cells, but direct proof of this function has been lacking. To address this issue, HL-60 human promyelocytic leukemia cells were exposed to RII beta **antisense** synthetic oligodeoxynucleotide, and the effects on cAMP-induced growth regulation were examined. Exposure of these cells to RII beta **antisense** oligodeoxynucleotide resulted in a decrease in cAMP analog-induced growth inhibition and differentiation without apparent effect on differentiation induced by phorbol esters. This loss in cAMP growth regulatory function correlated with a decrease in basal and induced levels of RII beta protein. Exposure to RII beta sense, RI alpha and RII alpha **antisense**, or irrelevant oligodeoxynucleotides had no such effect. These results show that the RII beta regulatory subunit of protein kinase plays a critical role in the cAMP-induced growth regulation of HL-60 leukemia cells.

L11 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
ACCESSION NUMBER: 1998:230916 BIOSIS

DOCUMENT NUMBER: PREV199800230916  
 TITLE: Growth inhibition of human ovarian cancer cells by differential modulation of protein kinase a isozymes.  
 AUTHOR(S): Seo, Jin; Kim, Se Nyun; Lee, Gap Ryol; Kim, So Young; Park, Sang Dai; Hong, Seung Hwan [Reprint author]  
 CORPORATE SOURCE: Inst. Molecular Biol. and Genetics, Seoul Natl. Univ., Seoul 151-742, North Korea  
 SOURCE: Korean Journal of Biological Sciences, (June, 1997) Vol. 1, No. 2, pp. 389-394. print.  
 ISSN: 1226-5071.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20 May 1998  
 Last Updated on STN: 20 May 1998

AB We examined the effect of modulation of PKA isozymes on the growth of human ovarian cancer cells. Three ovarian cancer cell lines, 2774, SK-OV-3, and OVCAR-3, were examined in this study. The treatment of 5  $\mu$ M 8-Cl-cAMP, which has been known to down regulate RI (or type I **PKA**) and up-regulate **RII** (or type II **PKA**), markedly inhibited the growth of all cell lines (50-80% at day 6). To test whether alteration in PKA regulatory subunits level can change the growth characteristics of ovarian cancer cells, we introduced RIIbeta- expression construct and RIalpha **antisense**-expression construct into 2774 cells. The overexpression of RIIbeta down-regulated RIalpha protein, and the **antisense**-expression of RIalpha up-regulated RIIbeta protein, showing that the intracellular levels of RI and RII are reciprocally regulated. In both cases, cell growth was reduced by 30% at day 2. These results indicate that the growth of ovarian cancer cells is controlled by the signals from PKA isozymes, and the modulation of PKA isozymes can be employed for the human ovarian cancer therapy.

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ACCESSION NUMBER: 1999:179705 SCISEARCH  
 THE GENUINE ARTICLE: 172BQ  
 TITLE: The type and the localization of cAMP-dependent protein kinase regulate transmission of cAMP signals to the nucleus in cortical and cerebellar granule cells  
 AUTHOR: Paolillo M; Feliciello A; Porcellini A; Garbi C; Bifulco M; Schinelli S; Ventra C; Stabile E; Ricciardelli G; Schettini G; Avvedimento E V (Reprint)  
 CORPORATE SOURCE: Univ Naples Federico II, Fac Med, Dipartimento Biol & Patol Cellulare & Mol, CNR, CEOS, Torre Biol 14 Fl, Via S Pansini 5, I-80131 Naples, Italy (Reprint); Univ Naples Federico II, Fac Med, Dipartimento Biol & Patol Cellulare & Mol, CNR, CEOS, I-80131 Naples, Italy; Univ Pavia, Fac Farm, Ist Farmacol, I-27100 Pavia, Italy; Univ Naples Federico II, Fac Med, Dipartimento Biochim & Biotecnol Med, I-80131 Naples, Italy; Fac Med, Ist Farmacol, Genoa, Italy; CBA, IST, Serv Farmacol & Neurosci, Genoa, Italy; Univ Catanzaro, Fac Med Catanzaro, Dipartimento Med Sperimentale, Catanzaro, Italy  
 COUNTRY OF AUTHOR: Italy  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (5 MAR 1999) Vol. 274, No. 10, pp. 6546-6552.  
 ISSN: 0021-9258.  
 PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 47  
 ENTRY DATE: Entered STN: 1999  
 Last Updated on STN: 1999

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB CAMP signals are received and transmitted by multiple isoforms of cAMP-dependent protein kinases, typically determined by their specific regulatory subunits. In the brain the major regulatory isoform RII beta and the RII-anchor protein, AKAP150 (rat) or 75 (bovine), are differentially expressed. Cortical neurons express RII beta and AKAP75; conversely, granule cerebellar cells express predominantly RI alpha and **RII** alpha. Cortical neurons accumulate **PKA** catalytic subunit and phosphorylated cAMP responsive element binding protein very efficiently into nuclei upon cAMP induction, whereas granule cerebellar cells fail to do so. Down-regulation of RII beta synthesis by **antisense** oligonucleotides inhibited cAMP-induced nuclear signaling in cortical neurons. Expression in cerebellar granule cells of RII beta and ARAP75 genes by microinjection of specific expression vectors, markedly stimulated cAMP-induced transcription of the lacZ gene driven by a cAMP-responsive element promoter.

These data indicate that the composition of PKA in cortical and granule cells underlies the differential ability of these cells to transmit cAMP signals to the nucleus.

L11 ANSWER 10 OF 19 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1993:486748 SCISEARCH

THE GENUINE ARTICLE: LP940

TITLE: DIFFERENTIATION THERAPY OF CANCER TARGETING THE RI-ALPHA REGULATORY SUBUNIT OF CAMP-DEPENDENT PROTEIN-KINASE (REVIEW)

AUTHOR: CHOCHUNG Y S (Reprint)

CORPORATE SOURCE: NCI, TUMOR IMMUNOL & BIOL LAB, CELLULAR BIOCHEM SECT, BLDG 10, ROOM 5B38, BETHESDA, MD 20892 (Reprint)

COUNTRY OF AUTHOR: USA

SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (AUG 1993)

Vol. 3, No. 2, pp. 141-148.

ISSN: 1019-6439.

PUBLISHER: INT JOURNAL ONCOLOGY, C/O PROFESSOR D A SPANDIDOS, EDITORIAL OFFICE, 1, S MERKOURI ST, ATHENS 116 35, GREECE.

DOCUMENT TYPE: General Review; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 86

ENTRY DATE: Entered STN: 1994

Last Updated on STN: 1994

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Consideration of the cancer process as a problem of blocked ontogeny makes attractive the approach to the control of cancer through differentiation therapy. The use of **antisense** strategy and retroviral vector-mediated gene transfer technology provided direct evidence that two isoforms of cAMP receptor protein, the RI and **RII** regulatory subunits of **cAMP-dependent protein kinase**, have opposite roles in cell growth and differentiation, RI being growth stimulatory while RII is a growth-inhibitory and differentiation-inducing protein. As RIalpha expression is enhanced during cell transformation, and in primary human tumors and cancer cell lines as compared to their normal counterparts, it is an attractive target for cancer treatment. 8-Cl-cAMP and RIalpha **antisense** oligodeoxynucleotide, those that effectively down-regulate RIalpha and upregulate RIIbeta without producing cytotoxicity, provide new approaches toward differentiation therapy of cancer.

L11 ANSWER 11 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2000326366 EMBASE



TITLE: Compensatory stabilization of RII( $\beta$ ) protein, cell cycle deregulation, and growth arrest in colon and prostate carcinoma cells by **antisense**-directed down-regulation of protein kinase A RI( $\alpha$ ) protein.

AUTHOR: Nesterova M.; Noguchi K.; Park Y.G.; Youl Nam Lee; Cho-Chung Y.S.

CORPORATE SOURCE: Y.S. Cho-Chung, National Cancer Institute, Building 10, 9000 Rockville Pike, Bethesda, MD 20892-1750, United States. chochung@helix.nih.gov

SOURCE: Clinical Cancer Research, (2000) Vol. 6, No. 9, pp. 3434-3441.  
Refs: 34  
ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20001005  
Last Updated on STN: 20001005

AB The cyclic AMP-dependent protein kinase (PKA) exists in two isoforms, PKA-I (type I) and PKA-II (type II), that contain an identical catalytic (C) subunit but distinct regulatory (R) subunits, RI and RII, respectively. Increased expression of RI( $\alpha$ )/PKA-I has been shown in human cancer cell lines, in primary tumors, in cells after transformation, and in cells upon stimulation of growth. We have shown previously that a single-injection RI( $\alpha$ ) **antisense** treatment results in a reduction in RI( $\alpha$ ) and PKA-I expression and sustained inhibition of human colon carcinoma growth in athymic mice (M. Nesterova and Y. S. Cho-Chung, Nat. Med., 1: 528-533, 1995). Growth inhibition accompanied reduction in RI( $\alpha$ )/PKA-I expression and compensatory increases in **RII**( $\beta$ ) protein and **PKA-II**( $\beta$ ), the **RII**( $\beta$ )-containing holoenzyme. Here, we report that these in vivo findings are consistent with observations made in cancer cells in culture. We demonstrate that the **antisense** depletion of RI( $\alpha$ ) in cancer cells results in increased RII( $\beta$ ) protein without increasing the rate of RII( $\beta$ ) synthesis or RII( $\beta$ ) mRNA levels. Pulse-chase experiments revealed a 3-6-fold increase in the half-life of RII( $\beta$ ) protein in **antisense**-treated colon and prostate carcinoma cells with little or no change in the half-lives of RI( $\alpha$ ), RII( $\alpha$ ), and C( $\alpha$ ) proteins. Compensation by RII( $\beta$ ) stabilization may represent a novel biochemical adaptation mechanism of the cell in response to sequence-specific loss of RI( $\alpha$ ) expression, which leads to sustained down-regulation of PKA-I activity and inhibition of tumor growth.

L11 ANSWER 12 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 138:147769 CA

TITLE: Use of **antisense** oligonucleotides to gene for **protein kinase A** regulatory subunit **RII** $\beta$  in therapy

INVENTOR(S): Monia, Brett P.; Wyatt, Jacqueline R.

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 98 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 221

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010283	A2	20030206	WO 2002-US22629	20020715

WO 2003010283 A3 20050203

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
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NE, SN, TD, TG

AU 9726244 A1 19971106 AU 1997-26244 19970624 <--

AU 713740 B2 19991209

US 6232463 B1 20010515 US 1998-128508 19980804 <--

US 2003083281 A1 20030501 US 2001-915485 20010725

PRIORITY APPLN. INFO.: US 2001-915485 A 20010725

AU 1993-38025 A3 19930225

US 1997-948151 A1 19971009

AB **Antisense** compds., compns. and methods are provided for modulating the expression of **protein kinase A** (**PKA**) regulatory subunit **RII $\beta$** . The compns. comprise **antisense** compds., particularly **antisense** oligonucleotides, targeted to nucleic acids encoding **PKA** regulatory subunit **RII** beta. Methods of using these compds. for modulation of **PKA** regulatory subunit **RII** beta expression and for treatment of diseases associated with expression of **PKA** regulatory subunit **RII** beta are provided.

L11 ANSWER 13 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 125:292111 CA

TITLE: Protein kinase A-directed **antisense** restrains cancer growth: sequence-specific inhibition of gene expression

AUTHOR(S): Cho-Chung, Yoon S.

CORPORATE SOURCE: Laboratory Tumor Immunology Biology, National Institutes Health, Bethesda, MD, 20892-1750, USA

SOURCE: Antisense & Nucleic Acid Drug Development ( **1996**), 6(3), 237-244

CODEN: ANADF5; ISSN: 1087-2906

PUBLISHER: Liebert

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 51 refs. summarizing the different roles for the two **protein kinase A** isoforms regulator subunits (**RI** and **RII**) in cell growth and differentiation. The review also describes the use of **antisense** oligonucleotide targeted to the **RI $\alpha$**  subunit mRNA in inhibiting cancer cell growth. Increased expression of the **RI $\alpha$**  subunit of cAMP-dependent protein kinase type I has been shown in human cancer cell lines, in primary tumors, in cells after transformation, and in cells upon stimulation of growth. The sequence-specific inhibition of **RI $\alpha$**  gene expression by an **antisense** oligodeoxynucleotide results in the differentiation of leukemia cells and growth arrest of cancer cells of epithelial origin. A single-injection **RI $\alpha$**  **antisense** treatment in vivo also causes a reduction in **RI $\alpha$**  expression and inhibition of tumor growth. Tumor cells behave like untransformed cells by making less protein kinase type I. The **RI $\alpha$**  **antisense**, which produces a biochem. imprint for growth control, requires infrequent dosing to restrain neoplastic growth in vivo.

L11 ANSWER 14 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 122:23295 CA

TITLE: The regulatory subunit of cAMP-dependent protein

AUTHOR(S): kinase as a target for cancer diagnosis and therapy  
Cho-Chung, Y.S.; Cereseto, A.; Budillon, A.; Clair,  
T.; Rohlf, C.  
CORPORATE SOURCE: Lab. Tumor Immunol. Biol., Natl. Cancer Inst.,  
Bethesda, MD, 20892, USA  
SOURCE: Mol. Oncol. Clin. Appl. (1993), 267-78.  
Editor(s): Cittadini, Achille. Birkhaeuser: Basel,  
Switz.  
CODEN: 59WEAC  
DOCUMENT TYPE: Conference  
LANGUAGE: English

AB The RI and RII regulatory subunit isoforms of **cAMP-dependent protein kinase** have opposite roles in cell growth and differentiation, i.e., RI is growth-stimulating while RII is growth-inhibiting and differentiation-inducing. RI expression is enhanced in human cancer cell lines and primary tumors so it is a potential target for cancer diagnosis and therapy. 8-Cl-cAMP, a site-selective cAMP analog, and RI **antisense** oligodeoxynucleotides which effectively down-regulate RI and upregulate RII, provide new approaches toward differentiation therapy of cancer.

L11 ANSWER 15 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 119:217813 CA  
TITLE: Thyroid-stimulating hormone-regulated growth and cell  
cycle distribution of thyroid cells involve type I  
isozyme of cyclic AMP-dependent protein kinase  
AUTHOR(S): Tortora, Giampaolo; Pepe, Stefano; Cirafici, Anna  
Maria; Ciardiello, Fortunato; Procellini, Antonio;  
Clair, Tim; Colletta, Giulia; Cho-Chung, Yoon Sang;  
Bianco, A. Raffaele  
CORPORATE SOURCE: Fac. Med. Chin., Univ. Napoli, Naples, 80131, Italy  
SOURCE: Cell Growth & Differentiation (1993), 4(5),  
359-65  
CODEN: CGDIE7; ISSN: 1044-9523  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Optimal growth and differentiation of normal rat thyroid FRTL5 cells depend strictly on the presence of TSH. FRTL5 cells deprived of TSH cease dividing and become quiescent. Addition of TSH to quiescent cells, which activates the cAMP-mediated pathway, is sufficient to stimulate cell entry into S phase of the cell cycle. The authors have previously shown that the differential expression of the 2 isoenzymes, type I and type II, of the cAMP-dependent protein kinase (PKA) correlates with cell growth and differentiation of several rodent and human cell lines. The authors have studied the role of PKA in the TSH-regulated growth and cell cycle distribution of FRTL5 cells. Upon addition of TSH to FRTL5 cells deprived of hormone, a rapid incubation of RI $\alpha$  (RI and RII are regulatory subunits of PKA) mRNA species occurred within 30 min after treatment, reaching the levels of proliferating FRTL5 cells at 12 h. RII $\alpha$  mRNA levels slightly increased after TSH addition, whereas C $\alpha$  mRNA levels did not show major changes. Photoaffinity labeling of PKA receptor proteins showed that addition of TSH to quiescent FRTL5 cells induced a progressive increase in RI $\alpha$  levels starting at 6 h after stimulation, whereas RII $\alpha$  receptor levels increased only slightly. When FRTL5 cells were treated with an **antisense** oligodeoxynucleotide targeted against the RI $\alpha$  regulatory subunit, their growth was arrested, whereas an **antisense** against the RII $\alpha$  regulatory subunit produced only a mild growth inhibition. Moreover, exposure to the **antisense** RI $\alpha$  oligomer resulted in accumulation of cells in the G0-G1 compartment, as during TSH deprivation. Unlike FRTL5 cells deprived of TSH, cells arrested by the specific RI $\alpha$  **antisense** oligomer failed to enter S phase upon stimulation with TSH. These results demonstrate that type I

isoenzyme of PKA is directly involved in TSH-regulated cell proliferation and may be involved in cell cycle distribution of thyroid FRTL5 cells.

L11 ANSWER 16 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 118:247063 CA

TITLE: An **antisense** oligodeoxynucleotide that depletes RI $\alpha$  subunit of cyclic AMP-dependent protein kinase induces growth inhibition in human cancer cells

AUTHOR(S): Yokozaki, Hiroshi; Budillon, Alfredo; Tortora, Giampaolo; Meissner, Scott; Beaucage, Serge I.; Miki, Keizaburo; Cho-Chung, Yoon S.

CORPORATE SOURCE: Cell. Biochem. Sect., Natl. Cancer Inst., Bethesda, MD, USA

SOURCE: Cancer Research (1993), 53(4), 868-72

CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Enhanced expression of the RI $\alpha$  subunit of cAMP-dependent protein kinase type I has been correlated with cancer cell growth. The authors provide evidence that RI $\alpha$  is a growth-inducing protein that may be essential for neoplastic cell growth. Human colon, breast, and gastric carcinoma and neuroblastoma cell lines exposed to a 21-mer human RI $\alpha$  **antisense** phosphorothioate oligodeoxynucleotide (S-oligodeoxynucleotide) exhibited growth inhibition with no sign of cytotoxicity. Mismatched sequence (random) S-oligodeoxynucleotides of the same length exhibited no effect. The growth inhibitory effect of RI $\alpha$  **antisense** oligomer correlated with a decrease in the RI $\alpha$  mRNA and protein levels and with an increase in RII $\beta$  (the regulatory subunit of protein kinase type II) expression. The growth inhibition was abolished, however, when cells were exposed simultaneously to both RI $\alpha$  and RII $\beta$  **antisense** S-oligodeoxynucleotides. The RII $\beta$  **antisense** S-oligodeoxynucleotide alone, exhibiting suppression of RII $\beta$  along with enhancement of RI $\alpha$  expression, led to slight stimulation of cell growth. These results demonstrated that two isoforms of cAMP receptor proteins, RI $\alpha$  and RII $\beta$ , are reciprocally related in the growth control of cancer cells and that the RI $\alpha$  **antisense** oligodeoxynucleotide, which efficiently depletes the growth stimulatory RI $\alpha$ , is a powerful biol. tool toward suppression of malignancy.

L11 ANSWER 17 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 112:31399 CA

TITLE: Human testis cDNA for the regulatory subunit RII $\alpha$  of a **cAMP-dependent protein kinase**

AUTHOR(S): encodes an alternate amino-terminal region  
Oeyen, Ole; Myklebust, Frode; Scott, John D.; Hansson, Vidar; Jahnsen, Tore

CORPORATE SOURCE: Inst. Pathol., Rikshosp., Oslo, Oslo, Norway

SOURCE: FEBS Letters (1989), 246(1-2), 57-64

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Phosphorylations catalyzed by cAMP-dependent protein kinase are essential for sperm motility, and type II cAMP-dependent protein kinase in mature sperm has been shown to be firmly bound to the flagellum via the regulatory subunit, RII. This study documents high-level expression of a human, testis-specific RII $\alpha$  mRNA (2.0 kb) analogous to the rat mRNA which is induced in haploid germ cells. Developed here are the mol. cloning of a full-length human cDNA corresponding to this unique testis mRNA, and the presence of an alternate amino-terminal region (amino acids

45-75) of the predicted RII $\alpha$  protein (404 amino acids) compared with the previously published mouse and rat sequences. However, this alternate region is also shown to be present in RII $\alpha$  mRNA (7.0 kb) of human somatic cells. The data indicate the divergent amino-terminal sequence to be due to species differences, suggesting an active evolutionary pressure on this particular region, which could be involved in subcellular attachment of RII $\alpha$  and thereby localization of kinase activity to certain targets within the cell.

L11 ANSWER 18 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 111:109940 CA

TITLE: Molecular cloning, complementary deoxyribonucleic acid structure and predicted full-length amino acid sequence of the hormone-inducible regulatory subunit of 3'-5'-cyclic adenosine monophosphate-dependent protein kinase from human testis

AUTHOR(S): Levy, Finn Olav; Oeyen, Ole; Sandberg, Maarten; Tasken, Kjetil; Eskild, Winnie; Hansson, Vidar; Jahnsen, Tore

CORPORATE SOURCE: Inst. Med. Biochem., Univ. Oslo, Oslo, N-0317, Norway

SOURCE: Molecular Endocrinology (1988), 2(12), 1364-73

CODEN: MOENEN; ISSN: 0888-8809

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A full-length cDNA clone for the hormone-inducible regulatory subunit RII $\beta$  (formerly called RII51) of type II cAMP-dependent protein kinase was isolated from a human testis cDNA library. The cloned cDNA demonstrated tissue-specific expression of RII $\beta$  mRNA in human tissues, with the highest mRNA levels in testis and ovary. The isolated human cDNA clone was 3.3-kb in length and contained 166 bp of G/C-rich 5'-noncoding sequence, an open reading frame of 1254-bp, and an A/T-rich 3'-nontranslated region containing 1836-bp followed by an 89 nucleotide long poly(A)-tail. The predicted protein contains 418 amino acids including the start methionine, and the estimated mol. weight of human RII $\beta$  is 53,856. The nucleotide sequence within the open reading frame and the predicted amino acid sequence of human RII $\beta$  are highly conserved compared with partial rat RII $\beta$  sequences, displaying 91% and 97% similarity, resp. Codon preference anal. of the cloned cDNA sequence indicated that the 2 cAMP-binding domains and the hinge region are highly conserved through evolution, whereas the dimerization domain displayed a codon preference pattern indicative of appearance at a later stage of evolution. The isolated human cDNA detected an FSH- and cAMP-inducible mRNA of 3.2-kb in rat Sertoli cells, thus confirming that the cloned cDNA represents the hormone-inducible regulatory subunit of cAMP-dependent protein kinase. This is the first report documenting the isolation of a full-length cDNA clone for the RII $\beta$  of **cAMP-dependent protein kinase**.

L11 ANSWER 19 OF 19 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 110:19423 CA

TITLE: Cloning and sequencing of cDNA for human **cAMP-dependent protein kinase** regulatory subunits RI $\alpha$  and RII $\beta$

INVENTOR(S): Jahnsen, Tore

PATENT ASSIGNEE(S): Norway

SOURCE: PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8803164	A1	19880505	WO 1987-NO69	19871027 <--
W: JP, NO, US				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
NO 8604301	A	19880429	NO 1986-4301	19861028 <--
US 5097026	A	19920317	US 1988-216715	19880628 <--
PRIORITY APPLN. INFO.:			NO 1986-4301	A 19861028
			WO 1987-NO69	W 19871027

AB The cDNAs for human cAMP-dependent protein kinase (A-PK) regulatory subunits RI $\alpha$  and RII $\beta$  are cloned and sequenced.